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EDITORIAL

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Ketogenic diet therapy for epilepsy: past 100 years of practice

Weijia Jiang[1], Jianxiang Liao[2], Dong Zhou[3] and Jie Mu[3*]

Ketogenic diet (KD) is a classic therapy for epilepsy, in addition to the therapeutic medicines and surgeries. KD as the treatment for epilepsy entered the 100th year.

The classic KD was proposed in the 1920s as a formula diet with a high proportion of fat (90%), a low proportion of carbohydrate, and appropriate proportions of protein and other nutrients, which does not affect normal growth and development, but is effective in treating some nervous system diseases, cancer and other diseases [1]. Except the classic KD, there are also three main variants of KD: medium-chain triglyceride, modified Atkins diet, and low glycemic index treatment. The variants of KD provide patients with boarder dietary choices. All KD types have shown efficacy against drug-resistant epilepsy, maintaining a good safety and tolerability profile [2]. In the recent review of KD for the treatment of drug-resistant epilepsy, more than 50% research results showed more than 50% patients had >50% seizure frequency reduction. Especially results in the infantile spasm had the higher rate. KD has remarkable effects in both pediatric and adult population with drug-resistant epilepsy [3] In China, KD has been used for the treatment of children drug-resistant epilepsy since 2004. The results are encouraged [4].

Although KD has a long history for treating drug-resistant epilepsy, there are still many challenges and questions awaiting solution. The mechanisms underlying the effect of KD on the nervous system remain unclear. Some studies have proposed neurotransmitters, brain energy metabolism, oxidative stress, and ion channels as key players in the process [5]. Recent research has shown that the gut microbiota mediates the KD effect in mice. KD and gut microbiota may have close relationships to prevent seizure [6]. There has been accumulating evidence for the efficacy of KD in the treatment of neurodegenerative diseases, malignant gliomas, drug-resistant epilepsy and other related nervous system diseases. However KD is increasingly recognized as effective therapies for nervous system diseases, there is a great insufficiency of rigorous and authentic controlled trials [5]. In addition, in some countries, especially economically underdeveloped countries, a high proportion of clinicians are not experienced in management of KD, and lack knowledge on the indications for KD, the initial treatment age of patients, and the basic treatment plan. Therefore, articles with regional situations, latest advances, theory updates, and professional guidance are helpful in improving this situation.

In the period of calling for paper about this special issue "Ketogenic Diet and Epilepsy Therapy", we provide a series of articles on the classic theory, latest advances, and regional practice of KD. Topics include KD practice situation in a country; analysis of factors influencing patients' compliance to KD; how KD adapts to the tastes of a particular part of a country; current situation of diet treatment of refractory epilepsy; expert advice on KD in the treatment of super-refractory status epilepticus; multi-center trial of KD for the treatment of refractory status epilepticus in children; effect of KD on a type of epilepsy; KD therapy for adult refractory epilepsy; neuroprotective effect of KD and its possible mechanism; assessment of efficacy of intravenous ketogenic injection in comparison to KD; effect of KD on intestinal flora of patients; and application of KD outside nervous system

*Correspondence: mujie2010@foxmail.com
[3] Neurology Department, West China Hospital of Sichuan University, 14# Third Section, Renmin Nan Road, Chengdu 610041, China
Full list of author information is available at the end of the article

diseases. Finally, according to the submitting, the thematic series present the topics centered around the KD (Fig. 1).

Currently, there is a lack of sufficient Chinese multicenter clinical research, and most of the recommendations on KD therapy are based on the work of International Ketogenic Diet Study Group. In this special issue, the article *Chinese expert recommendations on ketogenic diet therapy for super-refractory status epilepticus* by the CAAE Ketogenic Diet Commission largely fills this gap by describing clinical observation and expert experience based on studies in China. It also highlights the efforts in China to optimize and standardize the clinical use of KD for the treatment of super-refractory status epilepticus. This recommendation provides detailed guidance for clinicians concerning patient selection, timing of KD administration, diet implementation, selection of KD type, monitoring of adverse events, and follow-up treatment plans. As KD can be considered for patients of either sex at the age of over 1 month with a diagnosis of super-refractory status epilepticus and with no contraindications to KD, standardized use of ketogenic therapy is extremely important. Clinicians should have knowledge on the method of application, and scientists are encouraged to do further studies, especially prospective studies with a controlled design.

Infantile spasms (West syndrome) are a clinically common type of drug-resistant epilepsy syndrome with typical manifestations of spasms, hypsarrhthmia and psychomotor developmental delay. KD therapy has been applied as a new method for treating infantile spasm cases. In the paper entitled *A multicenter retrospective cohort study of ketogenic diet therapy in 481 children with infantile spasms,* a large multicenter retrospective cohort study was conducted in 17 tertiary hospitals in China to investigate the efficacy of KD therapy in the treatment of infantile spasms. This study was conducted from October 2014 to March 2020, including in 481 patients (including 308 males and 173 females) and compared the effect and retention rate at 1, 3, 6, and 12 months after the initiation of KD were recorded, and compared to the baseline during 4 weeks prior to KD treatment. Results showed that KD was effective in 62.8% of infantile spasms at 3 months of KD, with a seizure freedom rate of

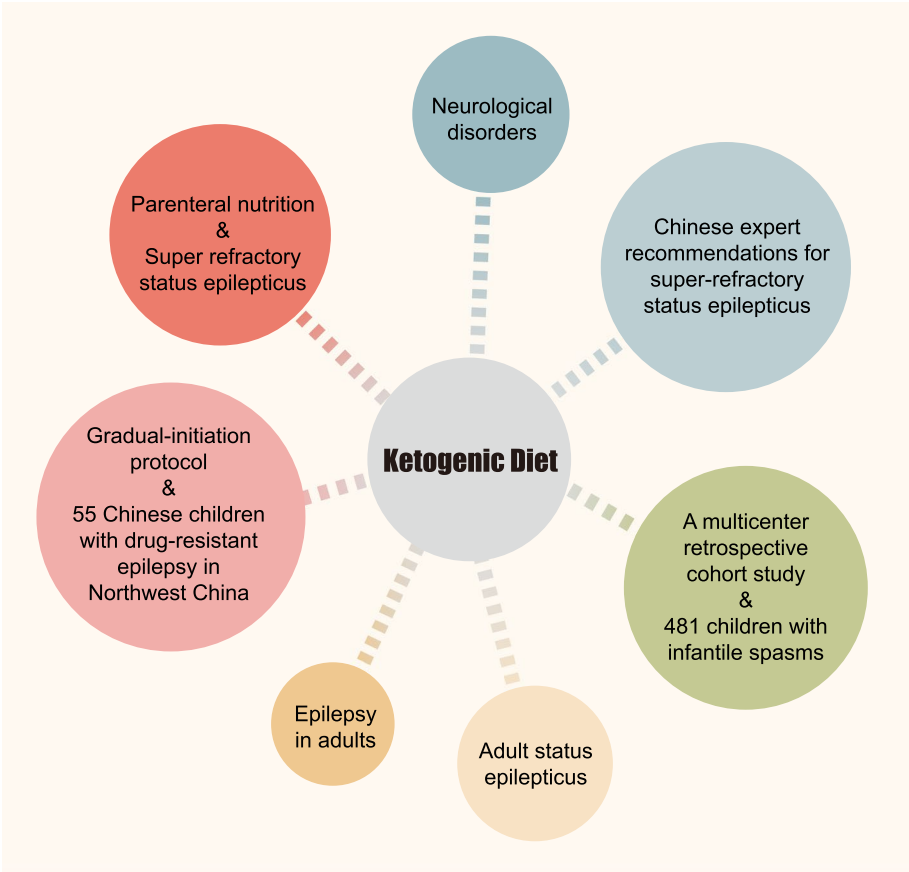

Fig. 1 Topics centered on ketogenic diet in this special issue

11.6% and the efficacy of KD for infantile spasms was not affected by medication, age, or glucocorticoid use before initiation. The adverse events mainly occurred during the first 3 months of KD, with gastrointestinal disturbance and constipation as the most common side effects. In this well-designed, retrospective, multicenter study, KD was proved effective in the treatment of infantile spasms with mild and acceptable side effects, thus being suitable for clinical application.

China is a big country with many different sub-cultures and eating habits. As people living in northwest China have a eating habit of consuming more carbohydrates, there are challenges for KD implementation in Northwest China. In the study entitled *Efficacy and tolerability of ketogenic diet therapy in 55 Chinese children with drug-resistant epilepsy in Northwest China,* the efficacy and tolerability of KD therapy in Chinese children with drug-resistant epilepsy in Northwest China were evaluated. The study lasted for 6 years in 55 children with drug-resistant epilepsy, aged from 2.2 months to 169.7 months (median, 14.1 months) at KD initiation. The efficacy of KD, reasons for discontinuation, duration of retention and rate of adverse events were evaluated. Of the 55 patients, 58.2% responded to the KD therapy at the last contact. Univariate analysis showed that the epilepsy and KD durations were predictors for KD effectiveness. Reasons for discontinuation of KD mainly included poor compliance and lack of response. Some side effects were observed with KD, most of which were minor. This article is a good attempt to discuss the application of ketogenesis in areas of different diet habits.

In this special issue, the review entitled *Recent aspects of ketogenic diet in neurological disorders* by Professor Heung Dong Kim, former chair of the Dietary Treatments Task Force of the International League Against Epilepsy, focused on recent aspects of KD use. Since its formal introduction in 1921 as a potent treatment for pediatric epilepsy, KD application has enter its 100th year of research. KD has definitive anti-seizure efficacy, safety, and feasibility in patients with epilepsy. The International Ketogenic Diet Study Group published consensus guidelines on practical information in 2009 and 2018. In this article, Kwon et al. reviewed recent aspects on the use of KD, including its mechanism of action, KD alternatives, its use across different age groups and regions, its use as a treatment for other neurological disorders, and future research perspectives. This paper provides important directions and values of KD research.

Despite the increasing numbers of available anti-seizure medications, the proportion of patients with drug-resistant epilepsy remains unchanged. KD is also an important choice for supplementary treatment in adults. However, during the treatment, the adult patients have poor adaptability to KD, and the side effects could be more serious. International recommendations for the treatment of adults receiving dietary therapy for epilepsy. In the review *Practical considerations of dietary therapies for epilepsy in adults*, Kaul et al. discuss on the specific aspects of care during management of adults receiving dietary therapy for epilepsy, including patient selection, dietary composition, initiation and monitoring, as well as the way and the timing of cessation of dietary treatment. In this review, the authors propose the need of a multidisciplinary team composed of well-trained dietitans and neurologists to provide care for patients during the dietary therapy. In future studies, the dietary composition should be optimized and the psychosocial needs of adults with epilepsy be addressed to improve the efficacy of KD and patient adherence to the dietary treatment.

Similarly, another review entitled *Ketogenic dietary therapy in adult status epilepticus: current progress and clinical application* by Professor Ding provides a comprehensive overview of the value of KD in adult status epilepticus patients, combining evidence from the latest randomized clinical trials and recommendations in practice guidelines. KD has been shown to be a safe and effective complementary therapy to current SE management in patients with drug-resistant epilepsy, based on evidence from several case reports and case series. KD plays a significant and beneficial role in the management of those critical patients. Besides, patients with status epilepticus have increased risk of infection and multiple organ failure due to their severe symptoms and complications. Therefore, in this review, the authors provide a comprehensive overview from the current applications and challenges, to the pre-treatment assessments, the contraindications, and to the assessments and monitoring. However, there are still some difficulties and challenges for clinical practice of KD such as enteral or parenteral form of KD. Intravenous administration of glucose is an essential nutritional support that might contradict the need for KD. Meanwhile, other drugs like glucocorticoids could inhibit the production of ketone bodies. The aim of this review was to provide a detailed management guidance for clinicians, patients, and their caregivers.

In this special issue, another article entitled *Calculation and management of ketogenic diet parenteral nutrition in super-refractory status epilepticus* focused on KD parenteral nutrition. Super-refractory status epilepticus is an important neurological emergency associated with high mortality and morbidity, which poses a heavy economic burden on patients and their families. Accumulating evidence has supported that ketogenic parenteral nutrition is an option for the treatment of super-refractory status

epilepticus when enteral feeding is temporarily limited or not possible. This review provides a comprehensive overview on contraindications, dietary prescription, treatment of adverse reactions, attentions and monitoring method for ketogenic parenteral nutrition management.

Abbreviations
KD: Ketogenic diet.

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Author details
[1]West China Medical Publishers, West China Hospital of Sichuan University, 14# Third Section, Renmin Nan Road, Chengdu 610041, China. [2]Neurology Department, Shenzhen Children's Hospital, 7019 Yitian Road, Futian District, Shenzhen 518038, China. [3]Neurology Department, West China Hospital of Sichuan University, 14# Third Section, Renmin Nan Road, Chengdu 610041, China.

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